JOC The Journal of Organic Chemistry

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Expansion of Thiele's Acid Chemistry in Pursuit of a Suite of Conformationally Constrained Scaffolds

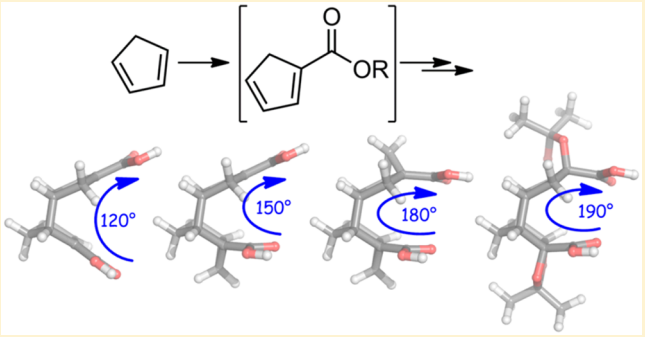
Jun Chen,[†] Brenden Kilpatrick,[†] Allen G. Oliver,[‡] and Jeremy E. Wulff*[,†]

[†]Department of Chemistry, University of Victoria, P.O. Box 3065 STN CSC, Victoria, BC V8W 3V6, Canada

[‡]Molecular Structure Facility, Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, Indiana, 46556, United States

Supporting Information

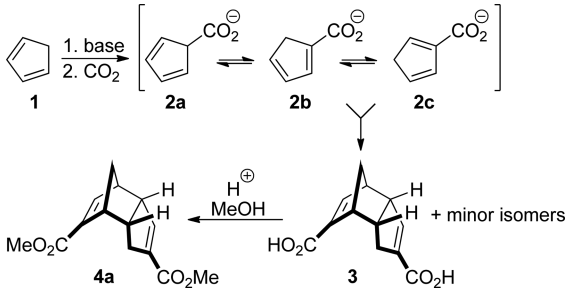
ABSTRACT: The Diels–Alder dimer of cyclopentadiene carboxylate, Thiele's acid has conformational properties that make it attractive as a molecular scaffold for applications in supramolecular and biological chemistry. However, a lack of known reaction methodology for derivatives of Thiele's acid (or the corresponding esters) has hampered its utilization in these fields. We describe an improved preparation of Thiele's esters and survey the chemistry of these versatile intermediates. As part of this effort, we also describe the synthesis of a suite of Thiele's acid (or ester) analogues spanning a broad range of cleft angles.



INTRODUCTION

Well over a century ago, Johannes Thiele reported that the reaction of cyclopentadienyl anion with carbon dioxide resulted in the formation of a dimeric product with the molecular formula $C_{12}H_{12}O_4$.[1,2] Subsequent studies revealed this product to be a mixture of regioisomeric Diels–Alder dimers, of which the major isomer produced was compound **3** (Scheme 1).[3]

Scheme 1. Thiele's 1901 Synthesis of a Diacid and Diester



Diacid **3**, which Thiele was able to purify by repeated crystallizations, is the result of an *endo* Diels–Alder coupling between two regioisomers of cyclopentadiene carboxylate, **2b** and **2c**, which may coexist with a third isomer, **2a**, in an equilibrating mixture.[4,5] Compound **3** is now known as Thiele's acid and represents a challenging test of the predictive power of mechanistic models used to forecast the outcomes of cycloaddition chemistry.[6,7]

Thiele's initial report went on to describe the conversion of diacid **3** to the corresponding diester **4a**, which could in turn be reacted with bromine to afford a tetrabromide derivative of formula $C_{14}H_{16}O_4Br_4$.[1] This early publication therefore provided a critical indication that productive chemical transformations could occur *both* at the two carbonyl functions *and* at the two olefins in what is otherwise a relatively unfunctionalized, rigid alkane scaffold.

From a structural perspective, Thiele's acid (or ester derivatives thereof; colloquially referred to as Thiele's esters) can be viewed as a *molecular cleft*: a rigid molecule containing a chemically inert backbone that projects functionality outward from its central core at a well-controlled angle.[8] It might be supposed, therefore, that products derived from **3** could find application in supramolecular systems (alongside better studied brethren like dibenzonorbornadienes,[9] terpyridines,[10] Kagan's ether,[11] and Tröger's base[12]), as a template for the preparation of ß-hairpin peptidomimetics[13] (akin to tetrahydrothiazolopyridinone,[14] amino(oxo)piperidinecarboxylate,[15] phenoxathiin,[16] or dibenzofuran[17] derivatives), or even as conformationally constrained enzyme inhibitors.[18]

A survey of the relevant literature, however, reveals three obstacles to the use of Thiele's acid and esters in these applications.

The first difficulty is that Thiele's acid itself is not terribly easy to access in pure form. Thiele's initial preparation suffered from low yields and required a series of recrystallizations to access pure **3**. Indeed, the purest compound was only obtained after esterification to **4a** and subsequent ester hydrolysis.[1] Marchand and Watson described a modified procedure that resulted in an improved yield (80% on 55 g scale) but noted that the product was contaminated with regioisomers even after

Received: June 12, 2015
Published: August 28, 2015

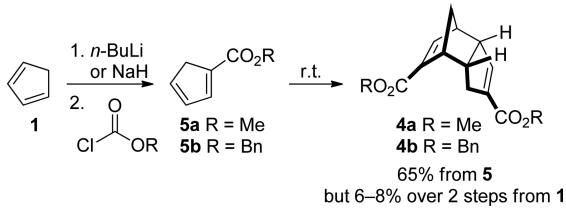
DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979–8989

recrystallization.[19] A subsequent publication from the same group indicated that selection of the major regioisomer required esterification, followed by recrystallization of diester **4a**.[20] Likewise, a report from the Smith group described the use of sodium sand for the initial deprotonation of cyclopentadiene, but the crude acid appears to have once again been taken on in impure form to the next step in the synthetic sequence.[21] In other cases, regioisomeric mixtures were inconsequential for the intended application, and so it appears that no effort was made to purify **3** to homogeneity.[22,23] Adding to this purification challenge is the fact that Thiele's acid is highly insoluble, an observation highlighted by the fact that despite over a century of chemistry on compound **3** we were unable to find any NMR spectral data for the pure compound in the literature.[24]

Esterification of **3** to **4a** prior to final purification might seem like it ought to be a fairly trivial exercise. However, two separate groups have reported the formation of unexpected addition products, either in the conversion of the acid to the methyl ester[21] or in the subsequent saponification of the ester back to the desired acid.[20]

An obvious strategy to avoid these difficulties would be to form the ester *prior* to dimerization. Indeed, methyl cyclopentadiene-1-carboxylate (**5a**) was reported by Peters to dimerize spontaneously to Thiele's ester **4a** at room temperature (Scheme 2).[25] However, this result obscures the fact that

Scheme 2. Direct Access to Thiele's Ester from the Corresponding Cyclopentadiene



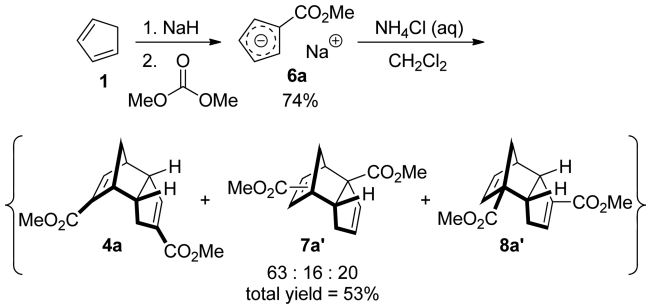
the monomeric ester itself is both volatile and unstable. The difficulty in accessing **5a** directly is highlighted by the fact that Peters actually generated this compound *by depolymerization of* ***4a***! We attempted to prepare Thiele's methyl and benzyl esters (**4a** and **4b**) directly by reaction of lithium or sodium cyclopentadienide and the appropriate chloroformate[26] but found that we consistently obtained yields of <10% over two steps. Minor regioisomers (separated from **4** by column chromatography) accounted for only a few additional percent, indicating that most of the poor yield was attributable to difficulties in handling **5**.

A recent publication from Dive and co-workers described a modification to this "ester first" approach,[27] wherein the metal salt of **5a** (i.e., **6a**, Scheme 3) was first isolated as a stable solid. The intermediate salt was then exposed to ammonium chloride to trigger reprotonation and subsequent dimerization.[27]

Although Dive's experimental conditions did not afford preparatively useful quantities of **4** in our hands, we nonetheless found this to be an excellent starting point for optimization and report here an improved synthetic protocol that provides gram-scale quantities of regioisomerically pure Thiele's ester.

The second obstacle to the use of Thiele's acid or esters in the applications described above is that a dearth of general reaction chemistry has been reported for this system, although the photochemically promoted intramolecular [2 + 2] cyclo-

Scheme 3. Dive's Salt Route to 4a[a]



[a]The structures shown for **7a**′ and **8a**′ are those assigned by Dive. See below for a re-interpretation of the structural assignments.

addition of **4a** was shown by Dunn and Donohue to afford the corresponding cyclobutane,[3] which was subsequently utilized by Marchand in the synthesis of a larger cage structure.[28] In addition, Deslongchamps and co-workers converted the diacid **3** to the corresponding ketone, en route to a synthesis of triquinacene;[29] the route was later repeated by the Paquette group to prepare a series of triquinacene derivatives for absorption and circular dichroism studies.[30] Notwithstanding these seminal contributions, however, very little (nonphotochemical) reactivity has been described for the two alkenes **3** or **4**, aside from Thiele's initial description of perbromination of **3**[1] and Peters' report of hydrogenations and epoxidations occurring at both alkenes of **4**.[31] However, in neither of these cases were the structures of the products established.

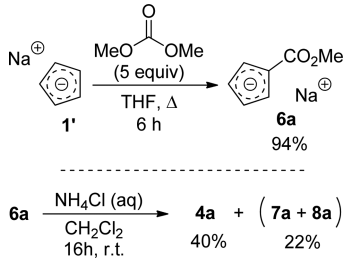
The third barrier to the use of Thiele's acid in supramolecular or medicinal applications is that the cleft angle (i.e., the difference between the vectors of projection for the two carbonyl functions in **3**) has not been shown to be tunable.

In the current work, we sought to address each of these obstacles by (1) establishing an improved, scalable route to regioisomerically pure **3** and **4**, (2) exploring the fundamental, nonphotochemical reaction chemistry of compound **4**, focusing particularly on selective transformations of the two alkenes, and (3) synthesizing and structurally characterizing a suite of derivatives of **4** containing a range of cleft angles.

RESULTS AND DISCUSSION

We began our studies by optimizing the preparation of Dive's salt (**6a**, Scheme 3). We found that an improved yield could be obtained by using commercially available sodium cyclopentadienylide (2.0 M in THF) and 5 equiv of dimethyl carbonate (Scheme 4). The desired salt was isolated by partial concentration of the reaction mixture, precipitation, and vacuum filtration to provide a 94% yield of **6a** on a 5.5 g

Scheme 4. Improved Preparation of the Intermediate Salt



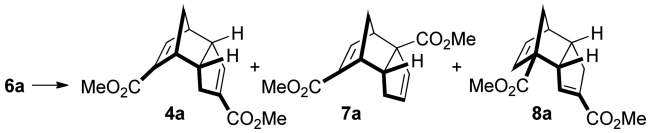
DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979–8989

scale. Although somewhat air and moisture sensitive, we found **6a** to be relatively stable under an argon atmosphere.

Exposure of **6a** to the conditions described by Dive (aqueous ammonium chloride in dichloromethane) provided a 40% isolated yield of **4a** after column chromatography, together with a further 22% of an approximately 1:1 mixture of regioisomers **7a** and **8a**.

Seeking to further optimize the synthesis of **4a**, we explored the effect of different solvents, temperature, reaction time and acid source on the yield of the reaction. As shown in Table 1,

Table 1. Optimization of Thiele's Ester Formation



	solvent	scale[a] (mg)	acid	temp (°C)	crude ratio **4a**: **7a**: **8a**	isolated yield of **4a** (%)
1	MeCN	500	AcOH[j]	rt[h]	100:21:22	39[b]
2	MeCN	250	AcOH[j]	50[g]	100:24:21	53
3	MeOH	250	NH_4Cl[j]	rt[i]	100:18:13	27[b]
4	MeOH	250	H_2SO_4[k]	rt[i]	100:17:14	38[b]
5	MeOH	250	H_2SO_4[k]	50[g]	100:15:13	48
6	MeOH	250	H_2SO_4[k]	50[i]	n.d.	46
7	toluene	250	AcOH[j]	50[g]	100:31:36	42
8	toluene	250	AcOH[j]	110[c,g]	n.d.	0[e]
9	DMSO	250	AcOH[j]	50[g]	100:26:36	28
10	*d*	250	AcOH[j]	50[i]	100:50:19	33
11	AcOH	250	AcOH[j]	50[g]	n.d.	38
12	THF	250	AcOH[j]	50[g]	n.d.	41
13	Et_2O	250	AcOH[j]	rt[i]	100:32:42	41[b]
14	CH_2Cl_2	250	AcOH[j]	40[c,h]	100:33:38	49
15	EtOAc	250	AcOH[j]	50[g]	100:35:44	52
16	iPrOH	250	H_2SO_4[k]	50[g]	100:19:18	56
17	2-pentanol	250	H_2SO_4[k]	50[g]	100:23:21	60
18	iPrOH	500	AcOH[j]	50[g]	100:22:24	56
19	iPrOH	500	*p*-TsOH[j]	50[g]	100:24:27	48
20	iPrOH	500	H_2SO_4[k]	83[c,g]	100:13:9	<58[f]
21	iPrOH	1750	H_2SO_4[k]	50[g]	n.d.	63
22	iPrOH	5000	H_2SO_4[k]	50[g]	n.d.	64

[a]Mass of **6a** used. [b]Calculated yield, accounting for minor impurities in the isolated product. [c]Reflux temperature for the solvent. [d]This reaction was conducted in the absence of additional solvent. [e]Extensive decomposition precluded the isolation of any pure compound. [f]This product contained an unidentified impurity. [g]The reaction was run for 16 h. [h]The reaction was run for 48 h. [i]The reaction was run for 72 h. [j]1.05 equiv of the acid source was used. [k]0.55 equiv of the acid source was used.

the use of a somewhat elevated temperature (50 °C) provided a modest benefit to the yield and purity of the isolated compound (e.g., compare entry 1 with entry 2 or entry 4 with entry 5). However, more extreme temperatures (e.g., entry 8) led to extensive decomposition. We therefore selected 50 °C as the optimal temperature for our other trials.

The acid source had little evident effect on the outcome of the reaction (e.g., compare entries 1, 3, and 4), while longer reaction times provided no increase in yield (compare entry 6 with entry 5). We found that the dimerization proceeded in several different solvents (entries 9−15), with modest but significant differences in both yield and product distribution. Relatively poor yields were found with DMSO or acetic acid as solvent, while aprotic solvents generally supported a higher incidence of unwanted regioisomers **7a** and **8a**.

Hindered alcohols were best for the reaction, with 2-propanol (entry 16) outperforming methanol (entry 5). 2-Pentanol was better still (entry 17), but the greater cost for this solvent led us to select 2-propanol as the medium of choice for the transformation.

We briefly re-examined the effect of the acid promoter but once again found no significant difference between acetic acid (entry 18) and sulfuric acid (entry 16). Addition of *p*-toluenesulfonic acid (entry 19) was associated with a reduced yield. The use of elevated temperatures (refluxing 2-propanol, entry 20) gave no increase in yield while diminishing the purity of the isolated product. Finally, we explored the effect of scale and were pleased to find that the reaction could be run on 5 g batches of **6a** with no loss in yield (entry 22).

Having achieved our initial goal of a scalable synthesis of compound **4**, we turned our attention to the characterization of the minor regioisomers **7** and **8**. The exact structures of these products (or their acid analogues) have been a matter of some disagreement, with several conflicting reports appearing in the literature. For example, an early report by Peters (relying mostly upon characterization by UV spectroscopy) tentatively assigned the structure of a minor regioisomer arising from the dimerization of cyclopentadiene carboxylate (**2**) as being the diacid congener of **8a-A** (Figure 2).[31] Later work by Marchand[19] suggested that Peters had actually characterized the precursor to **7a-A** (Figure 1) but that the acid forms of both **8a-A** and **7a-A** were present in the reaction mixture, at 13% and 1%, respectively.[19] Jaouen, on the other hand, proposed that the most abundant minor reaction product arising from dimerization of **2** was actually the diacid analogue of **7a-C**.[5] Most recently, Dive reported that the dimerization of the cyclopentadiene methyl ester (**6a**) gave two products in addition to the target compound **4a**. For one of these (shown as **7a**′ in Scheme 3), the position of the conjugated ester was left undefined (i.e., the proposed structure was either **7a-A** or **7a-B**). For the other regioisomer (shown as **8a**′ in Scheme 3) the structure **8a-C** was suggested.[27]

The multigram-scale synthesis of **4a** shown in Table 1 provided us with ample quantities of the two minor regioisomers **7a** and **8a**, which were spectroscopically identical to those isolated by Dive. Looking to establish once and for all the identity of these compounds, and to address any possibility that the dimerization of the ester **6a** might actually give rise to a different collection of regioisomers from that reported for the dimerization of **2**, we collected an extensive series of 1D and 2D NMR spectra for each isolated compound (^{1}H, ^{13}C, COSY, NOESY, HSQC, HMBC, TOCSY) and also performed DFT calculations[32] to calculate likely chemical shifts for each of the four possible structures for each isolated product (**7a-A**−**7a-D** and **8a-A**−**8a-D**) shown in Figures 1 and 2.

For the first minor regioisomer, **7a**, the NMR analysis was made significantly more challenging by the number of long-range couplings arising from the rigidity of the molecule (particularly the 4J couplings in the HMBC data), but we were ultimately able to determine the compound's identity as **7a-A**. Each of the other possible structures could be ruled out by the observation of at least one conflicting correlation in the HMBC spectrum, while **7a-C** and **7a-D** could be further eliminated on the basis of comparison to the calculated ^{13}C chemical shift data, wherein the expected shifts for C3a and C7a were >10

DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979−8989

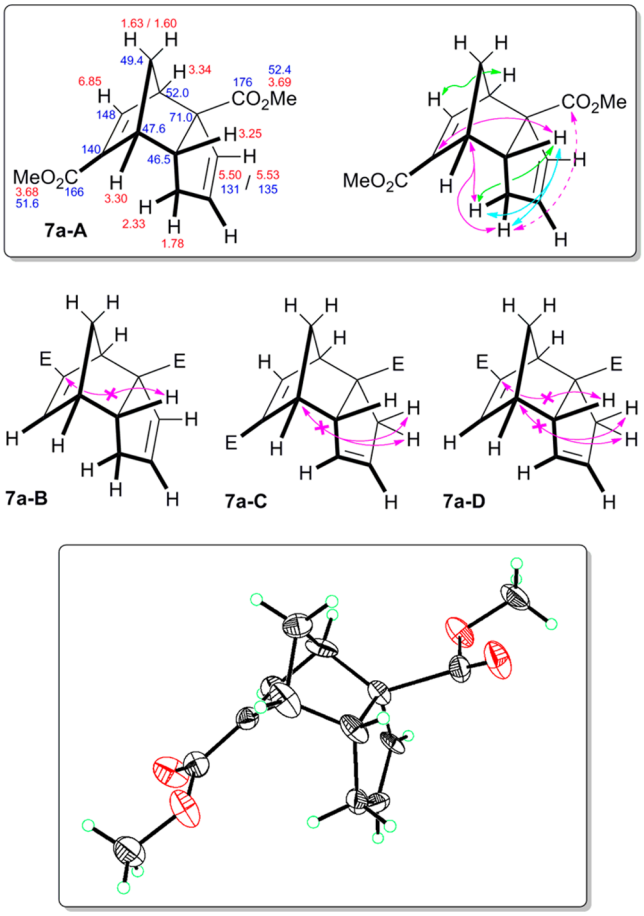


Figure 1. Structural assignment for **7a**: blue, ^{13}C chemical shifts; red, ^{1}H chemical shifts; green, COSY correlations; cyan, TOCSY correlations; solid mauve, 3J HMBC correlations: dashed mauve, 4J HMBC correlations. Only the most significant correlations are shown from each data set. Crosses indicate data that would be incompatible with the proposed structures.

ppm away from the observed signals (see Scheme 6 for atom numbering). Our assignment of **7a-A** as the correct structure for the first isolated regioisomer was further supported by the collection of X-ray data for an isolated crystal (inset to Figure 1). While this structure is of low quality due to internal disorder, it is nonetheless sufficient to confirm that the two ester functions exist on opposite faces of the molecule.

Turning to the second regioisomer, structures **8a-B** and **8a-C** could be quickly ruled out on the basis of HMBC data, but it was more difficult to unambiguously distinguish between structures **8a-A** and **8a-D**. Ultimately, however, **8a-D** was ruled out on the basis of the peak shape of the vinyl proton at 6.58 ppm in the ^{1}H NMR spectrum. This signal appears as an approximate quartet with a ~2 Hz coupling. Such a coupling pattern is inconsistent with the calculated geometry-optimized structure for **8a-D**, where at least one larger coupling (>5 Hz) would be expected for the proton attached to the conjugated olefin. The preponderance of evidence therefore supports **8a-A** as the correct structure for the second isolated regioisomer. An NOE interaction between the methylene proton at 1.94 ppm and the alkene proton at 6.09 ppm confirmed that this structure was also an *endo* adduct.

Returning to our target dimer **4**, we next sought to apply our method to the synthesis of additional analogues. We found that

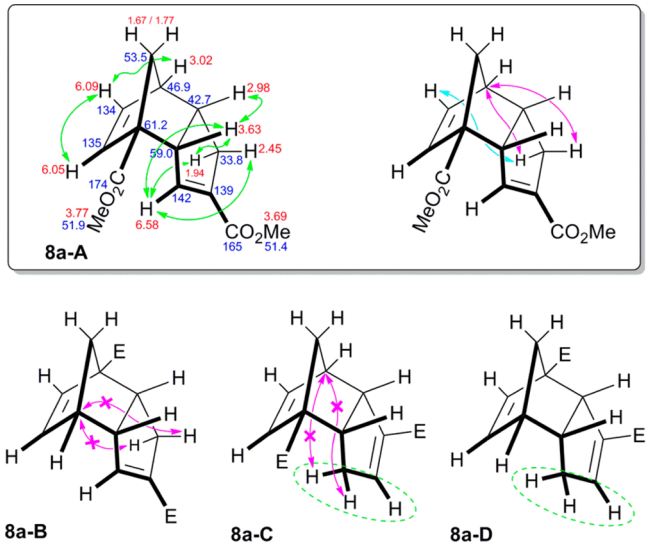


Figure 2. Structural assignment for **8a**: blue, ^{13}C chemical shifts; red, ^{1}H chemical shifts; green, COSY correlations; cyan, NOE correlations; mauve, HMBC correlations. Only the most significant correlations are shown from each data set. Crosses indicate data that would be incompatible with the proposed structures. Regions circled in green would be expected to contribute to couplings and peak shapes different from those observed in the ^{1}H NMR spectrum.

using dibenzyl carbonate in place of dimethyl carbonate furnished the corresponding benzyl ester **4b** (entry 1 of Table 2). However, the intermediate cyclopentadienylide salt

Table 2. Additional Thiele's Esters and Ketones

	electrophile	method [a]	product
1	BnO OBn (1.5 equiv)	B	**4b** 54%
2	(1 equiv)	A	**4c** 31%
3	(1 equiv)	A	**4d** 51%
4	(3 equiv)	B	**4e** 51%
5	Ph (3 equiv)	B	**4f** 35%

[a]Method A: the intermediate salt (**6**) was isolated by vacuum filtration, washed with ether, and dried prior to acidification in 2-propanol. Method B: the intermediate salt (**6**) was used directly in the acidification step. Refer to the Experimental section for details.

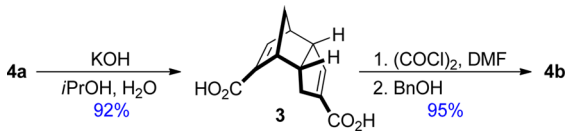
DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979−8989

(**6b**) was in this case too unstable to be isolated. In order to achieve a satisfactory yield of **4b**, we therefore adopted a modified procedure (method B) in which the intermediate salt was directly acidified to provide rapid conversion to the desired Diels–Alder product.

Because our primary interest is in using these Thiele's ester derivatives as scaffolds for various applications, we particularly desired to access compounds containing functional group handles for subsequent derivatization. In this vein, we were gratified to be able to access **4c** (containing terminal olefins for subsequent cross-metathesis reactions) and **4d** (containing primary alcohols for subsequent esterification reactions) in serviceable yields from diallyl carbonate and ethylene carbonate, respectively (entries 2 and 3). Using similar protocols, we also prepared two representative ketones, **4e** and **4f** (entries 4 and 5).[33] Unfortunately, attempts to use carbamates as electrophiles (to directly access the corresponding Thiele's amides) were not successful.

Hydrolysis and Fischer esterification of **4a** and **3**, respectively, have previously been reported to suffer from competing conjugate addition reactions.[20,21] We found that by conducting the hydrolysis reaction in a hindered solvent (Scheme 5) we could achieve high yields of regioisomerically

Scheme 5. Access to Regioisomerically Pure Thiele's Acid for Characterization by NMR Spectroscopy and Proof of Principle for Esterification



pure Thiele's acid (**3**). Notably, our NMR data (see Supporting Information) constitute the first complete spectral characterization for this century-old compound.[34] We also explored esterification from **3** back to **4** and found that prior formation of the corresponding bis-acyl chloride provided the desired ester in better yield and purity than the previously reported Fischer esterification strategy.

With scalable access to Thiele's acid and various ester derivatives well established, we next explored the reaction chemistry of **4a** (Scheme 6). We were particularly interested in identifying transformations that permitted the differentiation of the two conjugated alkenes (C2–C3 and C5–C6; see Scheme 6 for numbering) and of the two carbonyl functions (at C2′ and C6′).

Conjugate addition using benzylamine as a representative nucleophile proceeded solely at the C5–C6 alkene.[35,36] As expected, the nucleophile exclusively approached from the less-hindered face of the alkene, but the protonation step was less selective, affording a mixture of *anti* (**9**) and *syn* (**10**) addition products. Exposure of **9** to more DBU and higher temperature facilitated isomerization to the more stable **10**, although some elimination of benzylamine was also observed under these conditions. Repeated attempts to add nucleophiles to the C2–C3 alkene of **4a** or **10** were unsuccessful, leading us to suspect that this second alkene function does not experience the same degree of conjugation to the associated carbonyl group.[20,37] This observation is in good accord with previously reported computational studies[21] and indicated that functionalization of the Eastern portion of the molecule might be better achieved under electrophilic conditions. In the event, exposure of **10** to osmium tetraoxide-mediated dihydroxylation provided a 52% yield of the heavily functionalized product **11** as a single diastereomer.

Bis-alkene **4a** also reacted smoothly under dihydroxylation conditions to provide tetraol **12**. Once again focusing on transformations capable of distinguishing between the two similarly functionalized halves of the molecular framework, we were pleased to find that acetonide formation took place more rapidly at the Eastern diol of **12** to provide **13** in acceptable yield (after removal of overprotected product). Alternatively, the use of superstoichiometric concentrations of the acid catalyst (accompanied by a switch from *p*-toluenesulfonic acid to camphorsulfonic acid) afforded an excellent yield of the fully protected compound **14**. Hydrolysis of **14** was selective for the C2′ carboxyl group, providing **15** as an orthogonally functionalized scaffold.

We were able to prepare crystals of bis-ester **14** suitable for X-ray analysis. The resulting structure (inset to Scheme 6) provided a useful contrast to the known X-ray structure of **4a** (CCDC 704728).[38] As shown in Figure 3, the most striking effect of the $sp^2 \rightarrow sp^3$ hybridization change at C2 and C6 was to push the two ester functions inward, substantially narrowing the cleft angle between them (Figure 3).

The fact that **14** enforces a ca. 180° turn between the two carbonyl groups suggests that it could find application in the design of peptide β-turn mimics. At the same time, the *difference* in cleft angle between **4a** and **14** is quite large, and we wondered if we might be able to access compounds supporting intermediate angles in order to establish a more broadly applicable family of molecular scaffolds. Positing that the installation of 3-membered rings (formally sp^5 hybridized)[39] into the Thiele's acid structure would enforce a geometry at C2 and C6 that is midway between that of compounds **4a** (sp^2) and **14** (sp^3), we conducted a computational study to identify potentially valuable target compounds.

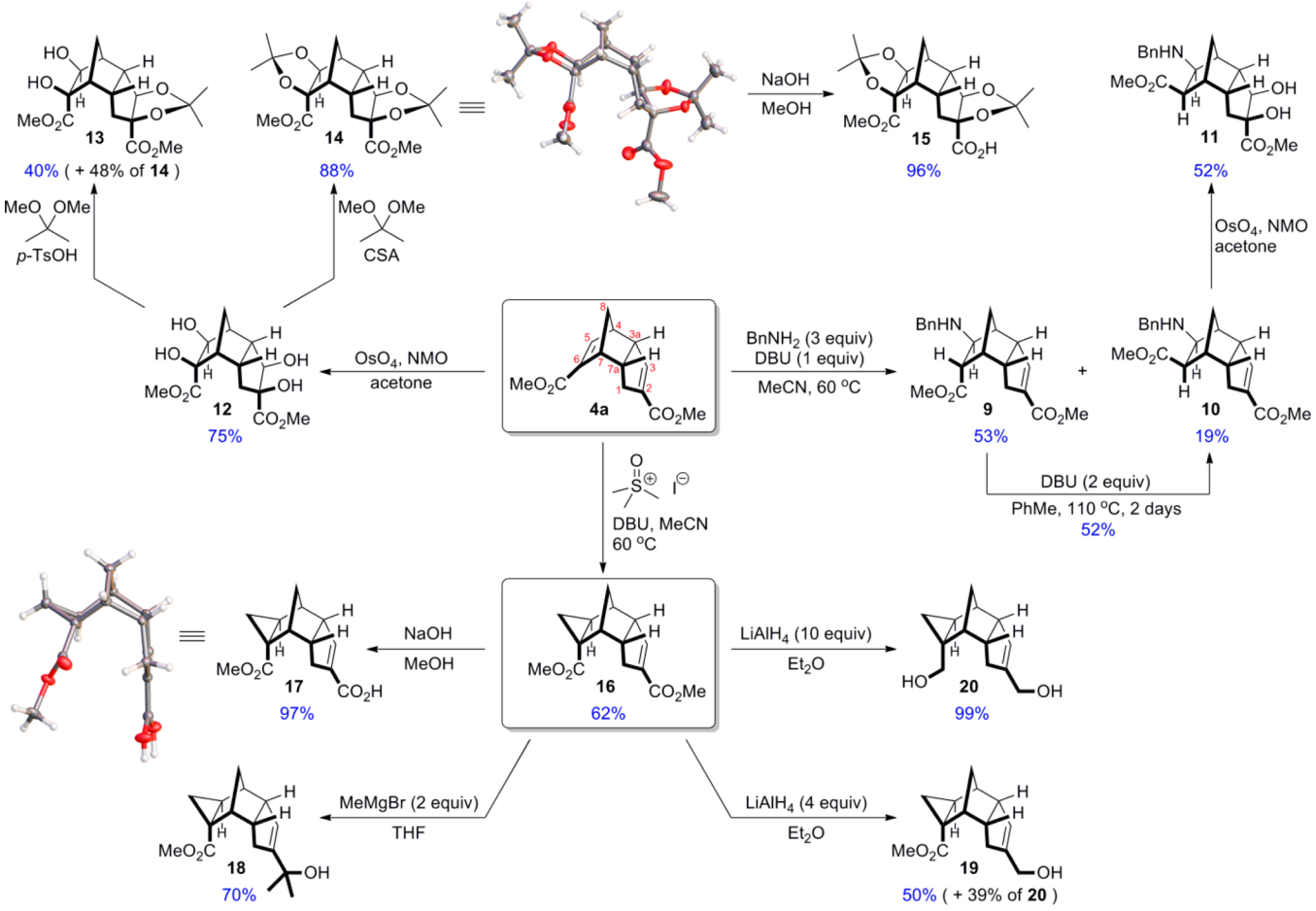
For the purpose of comparison (and to remove any conformational issues associated with the methyl ester groups in **4a** and **14**), we opted to conduct our study on diacids **A**–**D** (Table 3; red arrows indicate vectors of projection of the carboxyl groups from the central core). DFT calculations[40] indicated that calculated structure **A** (i.e., the in silico rendering of compound **3**) had a somewhat broader cleft angle (123°) than was observed for the solid-state structure of diester **4a** (133°). By contrast, calculated structure **D** (i.e., the in silico rendering of the diacid of **14**) had a somewhat narrower cleft angle (189°) than was observed for the solid-state structure of **14** (176°). These differences between our gas-phase calculations and solid-state structures may be at least partly due to packing effects in the crystals of **4a** and **14**.[41]

As hypothesized, structures **B** (incorporating a single cyclopropane) and **C** (incorporating two cyclopropanes) occupied structural space midway between the two extremes represented by **A** and **D**. We therefore adopted these molecules (or the corresponding half esters) as our final targets for synthesis.

As shown in Scheme 6, nucleophilic cyclopropanation of **4a** using the Corey–Chaykovsky protocol[42] exhibited the same level of selectivity as that shown in our previous conjugate addition reaction, taking place exclusively at the electrophilic C5–C6 alkene to afford compound **16** as a single regioisomer and single diastereomer. Saponification resulted in selective hydrolysis at the C2′ carboxyl group (analogous to our earlier result with **14**) to provide the desired target compound **17**.

DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979–8989

Scheme 6. Chemo- and Regioselective Derivatizations of Thiele's Ester in Pursuit of Scaffolds of Varying Cleft Angle



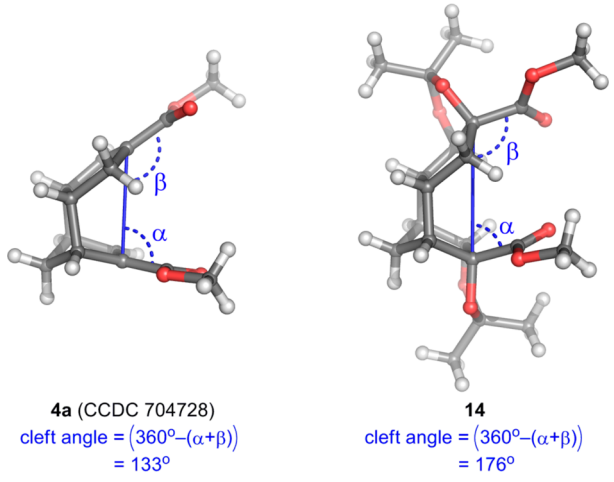


Figure 3. Comparison of X-ray data for **4a** and **14**.

Fortuitously, **17** was amenable to the production of X-ray quality crystals; the solved solid-state structure (inset to Scheme 6) confirmed the identity of the target compound and showed a cleft angle of 149°, nearly identical to that predicted for structure **B** in Table 3.

With significant quantities of intermediate **16** on hand, we also briefly explored other regioselective transformations. We found that Grignard addition took place exclusively at the C2′ carbonyl to afford compound **18** and that a partially selective reduction to provide compound **19** could be achieved by limiting the number of equivalents of reducing agent in the reaction mixture. Alternatively, when a larger excess of $LiAlH_4$ was added, complete reduction to diol **20** could be achieved in high yield.

Installation of the second cyclopropyl motif, to access our final target, **C**, was more challenging. Once again, the C2−C3 alkene proved resilient to the addition of nucleophiles, even under forcing conditions. Guided therefore by our earlier transformation of **10** to **11** under electrophilic dihydroxylation conditions, we explored the conversion of diol **20** to **21** using an electrophilic cyclopropanation (Scheme 7). Gratifyingly, we found that Simmons−Smith conditions[43] provided compound **21** in high yield, after which reoxidation of the two primary alcohols allowed access to the target diacid **22** (i.e., compound **C**).

Before completing our synthetic study, we wanted to address a limitation that we perceived for our methodology: the difficulty in hydrolyzing the C6′ ester (e.g., in **15** or **17**). While the reduction/reoxidation sequence that provided diacid **22** is always an option, it may not be sufficiently step-economical for some applications. An alternative route to a diacid product could be the hydrogenolysis of a benzyl ester precursor. Since we had ready access to compound **4b** (by two separate routes, described above), we sought to explore the synthetic utility of hydrogenolysis of a functionalized intermediate. We therefore converted **4b** to intermediate **23** (Scheme 7) using the same transformation that we had previously employed to access **16**.

DOI: 10.1021/acs.joc.5b01332
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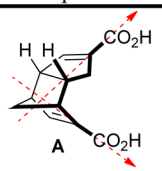
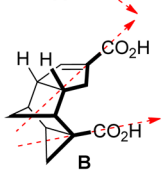
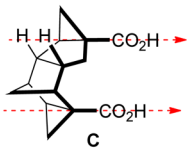
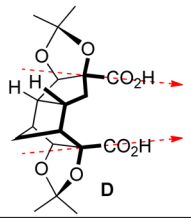
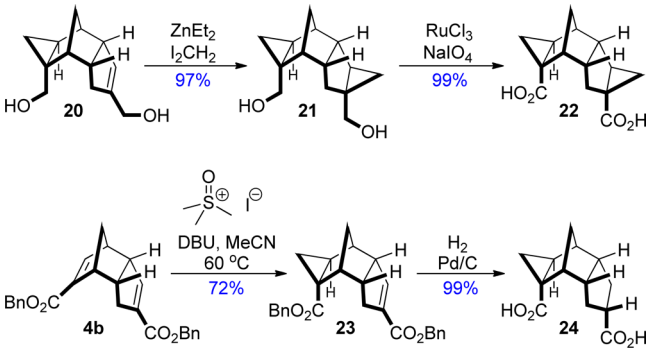
Table 3. Calculated Cleft Angles for Representative Scaffolds

compound[a]	α[b]	β[b]	cleft angle[c]
 A	105°	132°	**123°**
 B	81°	131°	**148°**
 C	80°	101°	**179°**
 D	68°	103°	**189°**

[a]See ref 40 for details. [b]Angles α and β are defined as illustrated in Figure 3. [c]The cleft angle is defined as = 360° − (α + β), such that a perfect reverse turn has a cleft angle of 180°.

Scheme 7. Access to Additional Scaffolds



As anticipated, standard hydrogenolysis conditions rapidly transformed both ester functions to the corresponding carboxylic acids while also reducing the remaining olefin. Diacid **24** was thus accessed in high yield.

CONCLUSIONS

Building upon existing synthetic methods, we have identified an improved protocol for the scalable synthesis of a variety of Thiele's esters, including novel structures like **4c** and **4d** that incorporate synthetic handles for the attachment of additional functionality. In addition, we have greatly expanded the repertoire of fundamental reaction chemistry for Thiele's esters, focusing particularly on selective transformations that permit one to discriminate between the two similarly functionalized halves of the scaffold structure. Generally speaking, we found the C5−C6 alkene to be amenable to a variety of selective nucleophilic transformations, after which the C2−C3 alkene could be reacted with electrophiles. Conversely, the C2′ ester function was much more reactive than the C6′ ester, although the use of benzyl ester intermediates permits dual reactivity when desired.

Along the way, we made important contributions to the structural assignment and characterization of the core Thiele's ester and acid building blocks: refining the structure of **7a**, revising the structure of **8a**, and recording the first NMR spectra for purified **3**.

Most significantly, we employed a combination of structure-based design (aided by both DFT calculations and X-ray crystallography) and strategic synthesis to establish a new suite of molecular scaffolds incorporating a broad range of cleft angles. We hope that the combination of easy synthetic access and structural tunability will lead these scaffolds to be employed in a diverse range of applications.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in single-neck, flame-dried, round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Liquid reagents were transferred via glass microsyringe. Solvents were transferred via syringe with a stainless steel needle. Organic solutions were concentrated at 40 °C by rotary evaporation under vacuum. Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with silica gel (0.20 mm, 60 Å pore-size, 230−400 mesh, Macherey-Nagel) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Flash-column chromatography was performed over silica gel 60 (63−200 μM, Caledon).

Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran was dried by distillation over sodium and benzophenone. Dichloromethane was dried by passage through alumina in a commercial solvent purification system (SPS).

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 or 500 MHz at ambient temperature. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26; D_2O, δ 4.79; DMSO-d_6, δ 2.50; MeOD, δ 3.31; acetone-d_6, δ 2.05). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 75 or 125 MHz at ambient temperature. Carbon chemical shifts are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.16; DMSO-d_6, δ 39.52; MeOD, δ 49.00; acetone-d_6, δ 29.84). Infrared (IR) spectra were obtained using an FT-IR spectrometer referenced to a polystyrene standard. Accurate masses were obtained using an ion trap MS. Melting points were obtained using a Mel-Temp II apparatus and are uncorrected.

General Procedure A. A flame-dried round-bottom flask fitted with an oven-dried condensor was charged with sodium cyclopentadienylide solution (2 M in THF, 1.0 equiv). To this solution was added the desired electrophile in THF at room temperature with stirring. The reaction mixture was heated to reflux for 6 h, cooled to room temperature, and concentrated in vacuo. The resulting solid was suspended in ether and collected by vacuum filtration. The collected solid was washed with ether until the washings became colorless and then dried in vacuo to give intermediate salt **6** as a tan-brown air-sensitive solid. In a separate step, the partially purified salt **6** (1 equiv) was added to a fresh round-bottom flask, where it was combined with iPrOH (to 0.33 M) and sulfuric acid (0.55 equiv) at room temperature with stirring. Acidification was marked by a brown to orange color change. The solution was heated to 50 °C overnight. The reaction mixture was concentrated in vacuo, and the resulting oil was dissolved in toluene and loaded onto a silica gel column. Elution with hexanes−ethyl acetate provided the desired Thiele's ester.

General Procedure B. A flame-dried round-bottom flask fitted with an oven-dried condensor was charged with sodium cyclopentadienylide solution (2 M in THF, 1.0 equiv). To this solution was

DOI: 10.1021/acs.joc.5b01332
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added the desired electrophile in THF at room temperature with stirring. The reaction mixture was heated to reflux for 6 h and then cooled to room temperature. The supernatant was transferred by cannula to a fresh round-bottom flask and concentrated in vacuo. To the resulting solid was added iPrOH (to 0.33 M) and sulfuric acid (0.55 equiv) at room temperature with stirring. Acidification was marked by a brown to orange color change. The solution was heated to 50 °C overnight. The reaction mixture was concentrated in vacuo, and the resulting oil was dissolved in toluene and loaded onto a silica gel column. Elution with hexanes−ethyl acetate provided the desired Thiele's ester.

Compound ***4a***. Prepared according to general procedure A using 20 mL of sodium cyclopentadienylide (2 M in THF, 40 mmol), 16.8 mL of dimethyl carbonate (100 mmol, in 20 mL THF), and 1.17 mL of H_2SO_4 (22 mmol, in 120 mL iPrOH). Chromatography (hexanes−ethyl acetate, 20:1) afforded 3.18 g (65%) of **4a** as a pale yellow solid (mp = 189−191 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 3.1 Hz, 1H), 6.49 (q, J = 2.2 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.44−3.52 (m, 1H), 3.32−3.37 (m, 1H), 3.10−3.14 (m, 1H), 2.91−3.01 (m, 1H), 2.47 (ddt, J = 17.9, 10.4, 2.0 Hz, 1H), 2.00 (ddt, J = 17.9, 4.0, 2.0 Hz, 1H), 1.67 (dt, J = 8.6, 1.7 Hz, 1H), 1.41 (dq, J = 8.8, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 165.4, 147.4, 142.8, 139.0, 138.1, 54.5, 51.6, 51.4, 51.0, 47.4, 46.8, 41.2, 33.1; IR (cm^{-1}, film) 2950, 1718, 1633, 1597, 1272, 1093, 765; HRMS (ESI) calcd for $[M + Na]^+$ $C_{14}H_{16}O_4Na$ 271.0941, found 271.0940.

Compound ***4b***. Prepared according to general procedure B using 2.5 mL of sodium cyclopentadienylide (2 M in THF, 5 mmol), 1.83 g of dibenzyl carbonate (7.5 mmol, in 5 mL THF), and 147 μL of H_2SO_4 (2.75 mmol, in 15 mL of iPrOH). Chromatography (hexanes−ethyl acetate, 5:1) afforded 540 mg (54%) of **4b** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 10H), 6.90 (d, J = 3.1 Hz, 1H), 6.55 (q, J = 2.1 Hz, 1H), 5.15 (s, 2H), 5.10 (q, J = 12.8, 6.0 Hz, 2H), 3.46−3.54 (m, 1H), 3.36−3.41 (m, 1H), 3.11−3.16 (m, 1H), 2.91−3.01 (m, 1H), 2.51 (ddt, J = 17.9, 10.4, 2.0 Hz, 1H), 2.10 (ddt, J = 17.9, 3.9, 2.1 Hz, 1H), 1.69 (dt, J = 8.8, 1.7 Hz, 1H), 1.41 (dq, J = 8.5, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 164.7, 148.0, 143.3, 138.9, 138.2, 136.5, 136.4, 128.6, 128.1, 128.0, 127.9, 66.1, 65.9, 54.5, 50.9, 47.5, 46.8, 41.2, 33.2; IR (cm^{-1}, film) 2944, 1708, 1454, 1268, 1231, 1074, 749; HRMS (ESI) calcd for $[M + H]^+$ $C_{26}H_{25}O_4$ 401.1748, found 401.1748.

Compound ***4c***. Prepared according to general procedure A from 2 mL of sodium cyclopentadienylide (2 M in THF, 4 mmol), 580 μL of diallyl carbonate (4 mmol, in 2 mL THF), and 117 μL of H_2SO_4 (2.2 mmol, in 3 mL of iPrOH). Chromatography (hexanes−ethyl acetate, 10:1) afforded 186 mg (31%) of **4c** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, J = 3.2 Hz, 1H), 6.54 (q, J = 2.2 Hz, 1H), 5.82−5.98 (m, 2H), 5.27 (dm, J = 17.3 Hz, 2H), 5.20 (dq, J = 10.4, 1.4 Hz, 2H), 4.63 (dq, J = 5.2, 1.5 Hz, 2H), 4.54−4.59 (m, 2H), 3.46−3.54 (m, 1H), 3.36−3.40 (m, 1H), 3.11−3.17 (m, 1H), 2.91−3.02 (m, 1H), 2.50 (ddt, J = 17.9, 10.4, 2.0 Hz, 1H), 2.06 (dtd, J = 17.9, 4.1, 2.2 Hz, 1H), 1.69 (dt, J = 8.8, 1.8 Hz, 1H), 1.36 (dd, J = 8.8,1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 164.6, 147.8, 143.1, 139.0, 138.2, 132.6, 132.5, 117.9, 117.8, 65.0, 64.9, 54.5, 50.9, 47.5, 46.8, 41.2, 33.2; IR (cm^{-1}, film) 2939, 1717, 1701, 1268, 1231, 1087, 765; HRMS (ESI) calcd for $[M + Na]^+$ $C_{18}H_{20}O_4Na$ 323.1254, found 323.1254.

Compound ***4d***. Prepared according to general procedure A from 5 mL of sodium cyclopentadienylide (2 M in THF, 10 mmol), 890 mg of ethylene carbonate (10 mmol, in 5 mL THF), and 293 μL of H_2SO_4 (5.5 mmol, in 7 mL iPrOH). Chromatography (hexanes−ethyl acetate, 2:1) afforded 786 mg (51%) of **4d** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J = 3.3 Hz, 1H), 6.54 (q, J = 2.1 Hz, 1H), 4.25−4.33 (m, 3H), 4.11 (ddd, J = 11.9, 4.8, 4.1 Hz, 1H), 3.77−3.84 (m, 4H), 3.49−3.56 (m, 1H), 3.37−3.41 (m, 1H), 3.15−3.20 (m, 1H), 2.91−3.01 (m, 1H), 2.61 (br, 2H), 2.48 (ddt, J = 17.9, 10.3, 2.0 Hz, 1H), 2.15 (dtd, J = 18.0, 3.9, 2.2 Hz, 1H), 1.68 (dt, J = 8.7, 1.8 Hz, 1H), 1.42 (dq, J = 8.5,0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 165.5, 148.5, 143.7, 138.3, 137.9, 66.2, 65.8, 61.6, 61.3, 54.3, 50.3, 47.5, 46.8, 41.0, 33.1; IR (cm^{-1}, film) 3416, 2943, 1707, 1630, 1272, 1235, 1068, 766; HRMS (ESI) calcd for $[M + Na]^+$ $C_{16}H_{20}O_6Na$ 331.1152, found 331.1148.

Compound ***4e***. Prepared according to general procedure B from 5 mL of sodium cyclopentadienylide (2 M in THF, 10 mmol), 2.4 mL of methyl acetate (30 mmol, in 5 mL of THF), and 293 μL of H_2SO_4 (5.5 mmol, in 10 mL of iPrOH). Chromatography (hexanes−ethyl acetate, 1:1) afforded 545 mg (51%) of **4e** as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, J = 3.3 Hz, 1H), 6.43 (q, J = 2.1 Hz, 1H), 3.52−3.60 (m, 1H), 3.42−3.48 (m, 1H), 3.17−3.22 (m, 1H), 2.86−2.93 (m, 1H), 2.39 (ddt, J = 18.0, 10.4, 2.0 Hz, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 1.85 (dtd, J = 18.1, 3.9, 2.0 Hz, 1H), 1.64 (dt, J = 8.7, 1.9 Hz, 1H), 1.42 (dq, J = 8.6,0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 195.7, 148.3, 147.5, 147.1, 142.6, 55.0, 50.5, 47.9, 45.6, 40.6, 32.6, 27.0, 25.7; IR (cm^{-1}, film) 2939, 1702, 1664, 1641, 1372, 1272, 950; HRMS (ESI) calcd for $[M + Na]^+$ $C_{14}H_{16}O_2Na$ 239.1042, found 239.1040.

Compound ***4f***. Prepared according to general procedure B from 5 mL of sodium cyclopentadienylide (2 M in THF, 10 mmol), 3.8 mL of methyl benzoate (30 mmol, in 5 mL of THF), and 293 μL of H_2SO_4 (5.5 mmol, in 15 mL of iPrOH). Chromatography (hexanes−ethyl acetate, 5:1) afforded 584 mg (35%) of **4f** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.63 (m, 2H), 7.51−7.56 (m, 2H), 7.44−7.50 (m, 2H), 7.30−7.37 (m, 4H), 6.62 (d, J = 3.3 Hz, 1H), 6.23 (q, J = 2.2 Hz, 1H), 3.66−3.73 (m, 2H), 3.27−3.32 (m, 1H), 3.03−3.14 (m, 1H), 2.70 (ddt, J = 18.2, 10.3, 1.9 Hz, 1H), 2.38 (dtd, J = 18.0, 3.8, 2.0 Hz, 1H), 1.82 (dt, J = 8.7, 1.7 Hz, 1H), 1.54 (dd, J = 8.8,0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 193.3, 150.4, 146.8, 146.3, 144.7, 138.8, 138.7, 131.9, 131.8, 129.1, 128.7, 128.6, 128.3, 128.2, 125.4, 55.4, 50.6, 48.6, 47.0, 40.8, 33.9; IR (cm^{-1}, film) 3060, 2938, 1687, 1636, 1578, 1446, 1353, 1277, 918; HRMS (ESI) calcd for $[M + Na]^+$ $C_{24}H_{20}O_2Na$ 363.1355, found 363.1357.

Compound ***7a***. Isolated as a yellow solid from the preparation of **4a** described above (540 mg; 11% yield; mp = 73−77 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (dd, J = 3.2, 1.3 Hz, 1H), 5.56 (dt, J = 5.7, 2.4 Hz, 1H), 5.48 (dt, J = 5.7, 2.3 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.30−3.35 (m, 2H), 3.21−3.28 (m, 1H), 2.40 (ddt, J = 18.3, 9.9, 2.2 Hz, 1H), 1.78 (dq, J = 18.3, 2.4 Hz, 1H), 1.65 (t, J = 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 165.7, 147.9, 139.7, 134.9, 130.0, 70.3, 52.3, 51.6, 51.3, 49.1, 46.9, 46.0, 34.6; IR (cm^{-1}, film) 2954, 1733, 1717, 1653, 1559, 1436, 1272, 1089, 773; HRMS (ESI) calcd for $[M + Na]^+$ $C_{14}H_{16}O_4Na$ 271.0941, found 271.0941.

Compound ***8a***. Isolated as a white solid from the preparation of **4a** described above (880 mg; 18% yield; mp = 98−102 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (q, J = 2.2 Hz, 1H), 6.09 (dd, J = 5.7, 2.7 Hz, 1H), 6.05 (d, J = 5.6, 2.7 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.60−3.67 (m, 1H), 2.96−3.05 (m, 2H), 2.45 (ddt, J = 17.6, 9.9, 2.1 Hz, 1H), 1.94 (dtd, J = 17.6, 3.6, 2.0 Hz, 1H), 1.77 (dd, J = 8.3, 1.8 Hz, 1H), 1.67 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 165.4, 142.2, 138.5, 134.6, 133.6, 61.2, 59.0, 53.5, 52, 51.5, 46.9, 42.7, 33.8; IR (cm^{-1}, film) 2955, 1734, 1718, 1653, 1559, 1275, 1096, 736; HRMS (ESI) calcd for $[M + Na]^+$ $C_{14}H_{16}O_4Na$ 271.0941, found 271.0941.

Compound ***3***. To a solution of Thiele's ester **4a** (270 mg, 1.1 mmol) in iPrOH (4 mL) was added KOH (10% solution, 4 mL) dropwise. After 5 h, iPrOH was removed in vacuo. The mixture was acidified to pH = 1 by addition of HCl (2 M) and extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford Thiele's acid **3** as a white powder without further purification (184 mg, 76%; mp >200 °C): ^{1}H NMR (300 MHz, D_2O) δ 6.60 (d, J = 3.1 Hz, 1H), 6.21 (q, J = 1.9 Hz, 1H), 3.39−3.48 (m, 1H), 3.13−3.20 (m, 1H), 3.04- 3.09 (m, 1H), 2.87−2.97 (m, 1H), 2.36 (ddt, J = 17.3, 10.5, 1.9 Hz, 1H), 1.88 (ddt, J = 17.3, 4.0, 2.0 Hz, 1H), 1.58 (dt, J = 8.4, 1.7 Hz, 1H), 1.36 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 174.7, 174.3, 143.8, 142.8, 139.6, 53.8, 50.3, 47.0, 46.9, 40.9, 34.0; IR (cm^{-1}, film) 2976, 2868, 1685, 1676, 1420, 1295, 1244, 949; HRMS (ESI) calcd for $[M + Na]^+$ $C_{12}H_{12}O_4Na$ 243.0628, found 243.0629.

Compounds ***9*** *and* ***10***. To a solution of Thiele's ester **4a** (100 mg, 0.40 mmol) in MeCN (3 mL) were added benzylamine (129.6 mg, 1.21 mmol) and DBU (61.4 mg, 0.80 mmol). The mixture was heated to 70 °C and stirred overnight. After being cooled to room temperature, the reaction was quenched by the addition of saturated

DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979−8989

NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 4:1) afforded 75 mg of **9** (53%) and 27 mg of **10** (19%). For compound **9** (brown solid; mp = 83−85 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.32 (m, 4H) 7.20−7.25 (m, 1H), 6.60 (q, J = 2.0 Hz, 1H), 3.74 (d, J = 12.8 Hz, 1H), 3.73 (s, 3H), 3.65 (d, J = 12.8 Hz, 1H), 3.62 (s, 3H), 3.25−3.30 (m, 1H), 3.24 (dd, J = 4.9, 1.7 Hz, 1H), 2.76 (t, J = 4.0 Hz, 1H), 2.70 (tt, J = 10.6, 4.0 Hz, 1H), 2.48−2.39 (m, 3H), 2.27 (ddt, J = 18.4, 3.1, 1.6 Hz, 1H), 1.86 (dt, J = 10.0, 1.4 Hz, 1H), 1.48 (dq, J = 10.0, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 165.3, 143.1, 140.7, 136.6, 128.4, 128.3, 127.0, 57.9, 54.6, 52.8, 52.1, 51.6, 51.5, 45.8, 44.3, 41.8, 40.5, 31.0; IR (cm^{-1}, film) 3436, 2959, 1720, 1639, 1438, 1273, 1081; HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{26}NO_4$ 356.1857, found 356.1860. For compound **10** (brown oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22−7.33 (m, 5H), 6.61 (q, J = 2.0 Hz, 1H), 3.76 (d, J = 12.3 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.66 (d, J = 12.3 Hz, 1H), 3.22−3.28 (m, 1H), 2.98 (dd, J = 8.1, 1.2 Hz, 1H), 2.69 (dd, J = 8.1, 1.2 Hz, 1H), 2.63 (ddt, J = 9.9, 4.2, 2.7 Hz, 1H), 2.53 (ddt, J = 17.5, 9.9, 2.5 Hz, 1H), 2.48 (d, J = 5.7 Hz, 1H), 2.37−2.44 (m, 2H), 2.07 (dt, J = 10.7, 1.6 Hz, 1H), 1.44 (dt, J = 10.6, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 165.4, 144.1, 140.7, 136.4, 128.4, 128.0, 127.0 60.6, 52.8, 52.5, 51.6, 51.5, 46.3, 44.2, 44.1, 41.6, 37.7, 31.4; IR (cm^{-1}, film) 3419, 2950, 1717, 1633, 1436, 1274, 1094; HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{26}NO_4$ 356.1857, found 356.1853.

*Isomerization of **9** to **10**.* To a solution of **9** (40 mg, 0.11 mmol) in toluene (3 mL) was added DBU (31 μL, 0.22 mmol). The mixture was heated to 110 °C and stirred for 2 d. After being cooled to room temperature, the reaction was quenched by the addition of saturated NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 4:1) afforded **10** as a brown oil (21 mg, 52%). Spectral details were identical to those provided above.

*Compound **11**.* To a solution of **10** (50 mg, 0.14 mmol) in 3 mL of acetone were added 4-methylmorpholine *N*-oxide (25.7 mg, 0.22 mmol) and OsO_4 (4% in H_2O, 45 μL, 0.007 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 6 h. The reaction was quenched by the addition of aqueous $Na_2S_2O_3$, and acetone was removed in vacuo. The resulting mixture was extracted twice with ethyl acetate, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 1:1) afforded **11** as a yellow oil (28 mg, 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13−7.29 (m, 5H), 4.07 (d, J = 8.6 Hz, 1H), 3.80 (d, J = 13.3 Hz, 1H), 3.77 (s, 3H), 3.69 (d, J = 13.3 Hz, 1H), 3.67 (s, 3H), 3.38 (dd, J = 8.3, 1.3 Hz, 1H), 2.94 (dd, J = 8.2, 1.4 Hz, 1H), 2.66 (ddd, J = 21.8, 9.4, 4.1 Hz, 1H), 2.28−2.40 (m, 3H), 2.22 (dt, J = 10.4, 1.8 Hz, 1H), 1.80 (dd, J = 14.1, 9.6 Hz, 1H), 1.70 (dd, J = 14.1, 9.6 Hz, 1H), 1.56 (d, J = 10.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 173.6, 140.5, 128.4, 128.0, 127.0, 86.2, 74.9, 58.9, 53.2, 52.9, 51.5, 50.8, 46.6, 42.3, 42.0, 41.1 33.4; IR (cm^{-1}, film) 3436, 2954, 1726, 1642, 1452, 1275, 1171, 1083, 748; HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{28}NO_6$ 390.1911, found 390.1908.

*Compound **12**.* To a solution of Thiele's ester **4a** (400 mg, 1.61 mmol) in 20 mL of acetone were added 4-methylmorpholine *N*-oxide (565 mg, 4.83 mmol) and OsO_4 (4% in H_2O, 1.02 mL, 0.16 mmol) at 0 °C. The reaction was quenched by the addition of aqueous $Na_2S_2O_3$, and acetone was removed in vacuo. The resulting mixture was extracted twice with ethyl acetate, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Chromatography (5% methanol in dichloromethane) afforded **12** as a yellow oil (382 mg, 75%): ^{1}H NMR (300 MHz, MeOD) δ 4.60 (d, J = 2.1 Hz, 1H), 4.25 (d, J = 8.7 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.65−2.79 (m, 1H), 2.39−2.51 (m, 2H), 2.35 (dt, J = 10.3, 1.7 Hz, 1H), 2.16−2.21 (m, 1H), 1.43−1.63 (m, 3H); ^{13}C NMR (75 MHz, MeOD) δ 175.3, 175.0, 87.2, 81.3, 75.6, 71.4, 52.7, 52.6, 51.0, 50.3, 46.2, 41.5, 41.3, 34.9; IR (cm^{-1}, film) 3408, 2959, 1728, 1644, 1439, 1273, 1073, 728; HRMS (ESI) calcd for $[M + Na]^+$ $C_{14}H_{20}O_8Na$ 339.1050, found 339.1049.

*Compounds **13** and **14**.* To a solution of **12** (64 mg, 0.20 mmol) in 3 mL of acetone were added 2,2-dimethoxypropane (0.4 mL) and *p*-toluenesulfonic acid (32 mg, 0.16 mmol). The reaction was stirred at room temperature overnight. Solvent was removed in vacuo, and the residue was purified by chromatography (hexanes−ethyl acetate, 1:1) to afford **13** (28 mg, 40%) and **14** (38 mg, 48%) as colorless oils. For compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (d, J = 1.9 Hz, 1H), 4.30 (t, J = 8.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.49 (s, 1H), 2.68−2.82 (m, 1H), 2.43−2.55 (m, 3H), 2.17 (d, J = 10.3 Hz, 1H), 2.12 (d, J = 9.0 Hz, 1H), 1.71 (dd, J = 14.5, 9.3 Hz, 1H), 1.53 (dd, J = 14.5, 10.4 Hz, 1H), 1.48 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 172.7, 110.4, 88.9, 85.8, 79.8, 74.1, 53.0, 52.6, 47.9, 47.0, 42.3, 40.7, 39.5, 32.3, 26.2, 25.8; IR (cm^{-1}, film) 3445, 2992, 2955, 1737, 1654, 1437, 1258, 1070, 731; HRMS (ESI) calcd for $[M + H]^+$ $C_{17}H_{25}O_8$ 357.1544, found 357.1544. For compound **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (d, J = 5.0 Hz, 1H), 4.93 (d, J = 1.9 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 2.93−3.05 (m, 1H), 2.70 (dt, J = 12.8, 5.1 Hz, 1H), 2.49−2.56 (m, 2H), 2.10−2.17 (m, 2H), 1.51 (s, 3H), 1.47−1.55 (m, 1H), 1.47 (s, 3H), 1.40 (d, J = 10.5 Hz, 1H)1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.1, 113.1, 110.7, 96.5, 89.1, 82.1, 79.1, 52.6, 52.4, 51.7, 47.6, 44.5, 41.5, 40.1, 33.1, 29.2, 27.5, 26.4, 26.0; IR (cm^{-1}, film) 2990, 2953, 1742, 1457, 1373, 1256, 1072, 1036, 749; HRMS (ESI) calcd for $[M + Na]^+$ $C_{20}H_{28}O_8Na$ 419.1676, found 419.1674.

*Direct Access to Compound **14** from **12**.* To a stirred solution of **12** (90 mg, 0.28 mmol) in 4 mL of dichloromethane were added 2,2-dimethoxypropane (0.8 mL) and camphorsulfonic acid (160 mg, 0.68 mmol) at 0 °C. The reaction was allowed to warm to room temperature with stirring. After 16 h, the reaction mixture was cooled to 0 °C, and the reaction was quenched by the addition of aqueous $NaHCO_3$. The resulting mixture was extracted twice with dichloromethane, and the combined organic layers were dried over $NaSO_4$ and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 6:1) afforded **14** (103 mg, 88%) as a colorless oil with spectral properties identical to those reported above.

*Compound **15**.* To a stirring solution of **14** (44 mg, 0.11 mmol) in 1 mL of MeOH was added NaOH (10% solution, 1 mL) slowly. The reaction was stirred overnight. MeOH was removed in vacuo, and the mixture was acidified to pH = 1 by addition of aqueous HCl (2 M), extracted twice with ethyl acetate, dried over $MgSO_4$, and concentrated in vacuo to afford **15** as a white solid (41 mg, 96%, mp = 161−162 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, J = 4.9 Hz, 1H), 4.93 (d, J = 1.9 Hz, 1H), 3.75 (s, 3H), 2.93−3.06 (m, 1H), 2.71 (dt, J = 12.8, 5.0 Hz, 1H), 2.57 (d, J = 4.4 Hz, 1H), 2.51 (d, J = 4.4 Hz, 1H), 2.11−2.23 (m, 2H), 1.61 (dd, J = 16.2, 8.7 Hz, 1H), 1.53 (s, 3H), 1.47 (s, 3H), 1.42 (d, J = 11.9 Hz, 1H), 1.36 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 173.0, 113.6, 110.9, 96.3, 89.2, 82.3, 79.0, 52.8, 51.8, 47.6, 44.6, 41.6, 40.2, 33.2, 29.2, 27.7, 26.5, 26.1; IR (cm^{-1}, film) 3056, 2978, 2941, 1716, 1639, 1598, 1578, 1447, 1353, 1277, 732; HRMS (ESI) calcd for $[M + Na]^+$ $C_{19}H_{26}O_8Na$ 405.1520, found 405.1521.

*Compound **16**.* To a stirred solution of trimethylsulfoxonium iodide (273 mg, 1.24 mmol) and DBU (341 mg, 2.24 mmol) in MeCN (5 mL) was added Thiele's ester **4a** (140 mg, 0.56 mmol) in 1 mL of MeCN. The reaction mixture was heated to 60 °C for 36 h and then returned to room temperature. The resulting mixture was diluted with ethyl acetate, filtered through filter paper, and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by chromatography (hexanes−ethyl acetate, 4:1) to afford **16** as a white solid (91 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (q, J = 2.0 Hz, 1H), 3.68 (s, 3H), 3.57 (s, 3H), 3.19−3.27 (m, 1H), 2.62−2.75 (m, 3H), 2.53−2.58 (m, 1H), 2.40 (ddt, J = 18.7, 10.5, 2.7 Hz, 1H), 1.35 (dd, J = 7.7, 4.0 Hz, 1H), 1.22 (dt, J = 11.0, 1.6 Hz, 1H), 1.12 (dd, J = 5.1, 4.6 Hz, 1H), 0.89 (dd, J = 11.0, 1.2 Hz, 1H), 0.56 (dd, J = 7.7, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 165.4, 142.7, 137.4, 53.8, 51.5, 51.4, 44.5, 40.4, 39.8, 31.1, 30.9, 25.2, 21.5, 13.6; IR (cm^{-1}, film) 2954, 1707, 1442, 1293, 1230, 1150, 1095, 951; HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{19}O_4$ 263.1278, found 263.1276.

*Compound **17**.* To a stirring solution of **16** (41 mg, 0.16 mmol) in 1 mL of MeOH was added NaOH (10% solution, 1 mL) slowly. The

DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979−8989

reaction was stirred overnight. MeOH was removed in vacuo, and the mixture was acidified to pH = 1 by addition of aqueous HCl (2 M), extracted twice with ethyl acetate, dried over $MgSO_4$, and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 2:1) afforded **17** as a white solid (38 mg, 97%, mp = 193−196 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (q, J = 1.9 Hz, 1H), 3.61 (s, 3H), 3.22−3.31 (m, 1H), 2.65−2.79 (m, 3H), 2.59−2.62 (m, 1H), 2.43 (ddt, J = 18.6, 10.2, 2.6 Hz, 1H), 1.38 (dd, J = 7.7, 4.3 Hz, 1H),1.25 (dt, J = 11.0, 1.7 Hz, 1H), 1.15 (t, J = 5.0, Hz, 1H), 0.93 (dd, J = 11.1, 1.0 Hz, 1H), 0.60 (dd, J = 7.8, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 169.6, 145.5, 137.0, 54.0, 51.7, 44.6, 40.4, 39.9, 31.1, 30.6, 25.3, 21.6, 13.6; IR (cm^{-1}, film) 2935, 1710, 1673, 1423, 1295, 1129, 1116, 749; HRMS (ESI) calcd for $[M + H]^+$ $C_{14}H_{17}O_4$ 249.1122, found 249.1121.

Compound ***18***. To a solution of **16** (40 mg, 0.15 mmol) in THF (6 mL) was added MeMgBr (3.0 M in THF, 0.1 mL, 0.3 mmol) dropwise. The reaction was stirred overnight. The mixture was quenched by the addition of saturated NH_4Cl and extracted with ether. The aqueous layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 4:1) afforded **18** as a colorless oil (34 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (q, J = 1.9 Hz, 1H), 3.67 (s, 3H), 3.07−3.16 (m, 1H), 2.58−2.70 (m, 2H), 2.38−2.48 (m, 2H), 2.30 (ddt, J = 18.2, 10.1, 2.7 Hz, 1H), 1.81 (br, 1H), 1.43 (dd, J = 7.9, 4.6 Hz, 1H), 1.36 (s, 3H), 1.18−1.26 (m, 4H), 1.16 (t, J = 4.7 Hz, 1H), 0.91 (dd, J = 10.7, 1.0 Hz, 1H), 0.55 (dd, J = 7.6, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 152.8, 123.0, 70.0, 53.2, 51.9, 44.4, 40.4, 39.5, 31.4, 30.3, 29.6, 28.3, 25.6, 21.4, 14.2; IR (cm^{-1}, film) 3429, 2974, 1701, 1647, 1439, 1292, 1157, 750; HRMS (ESI) calcd for $[M + Na]^+$ $C_{16}H_{22}O_3Na$ 285.1461, found 285.1456.

Compounds ***19*** *and* ***20***. To a solution of **16** (162 mg, 0.62 mmol) in ether (10 mL) was added $LiAlH_4$ (58.7 mg, 2.48 mmol) at 0 °C. After addition, the reaction was warmed to room temperature and stirred overnight. The next day, the reaction was quenched by the addition of water, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 1:1 to 1:3) afforded **19** (72 mg, 50%) and **20** (49 mg, 39%). For **19** (colorless oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48−5.52 (m, 1H), 4.16 (dd, J = 12.7, 3.6 Hz, 1H), 3.90- 3.99 (m, 1H), 3.67 (s, 3H), 3.07−3.17 (m, 1H), 2.60−2.70 (m, 2H), 2.42−2.47 (m, 1H), 2.38 (d, J = 18.5 Hz, 1H), 2.20 (dd, J = 18.1, 9.7 Hz, 1H), 1.66 (dd, J = 8.2, 4.0 Hz, 1H), 1.43 (dd, J = 8.0, 4.6 Hz, 1H), 1.22 (dt, J = 11.0, 1.7 Hz, 1H), 1.14 (t, J = 5.1 Hz, 1H), 0.91 (dd, J = 11.0, 1.2 Hz, 1H), 0.53 (dd, J = 7.9, 5.2 Hz,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 145.7, 126.7, 62.2, 53.0, 51.9, 44.8, 40.4, 39.3, 31.7, 31.3, 25.5, 21.4, 14.0; IR (cm^{-1}, film) 3427, 2950, 1705, 1438, 1294, 1164, 1017, 923, 751; HRMS (ESI) calcd for $[M + Na]^+$ $C_{14}H_{18}O_3Na$ 257.1148, found 257.1148. For **20** (pale yellow crystalline solid, mp =105−110 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (s, 1H), 4.14 (s, 2H), 4.07 (dd, J = 11.6, 1.0 Hz, 1H), 3.22 (d, J = 11.6 Hz, 1H), 3.07−3.16 (m, 1H), 2.54−2.69 (m, 2H), 2.27−2.44 (m, 3H), 1.83 (br, 2H) 1.19 (dt, J = 10.7, 1.8 Hz, 1H), 0.77−0.85 (m, 3H), −0.12 (dd, J = 6.9, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 127.1, 66.6, 62.1, 52.9, 45.6, 40.5, 39.1, 33.5, 32.1, 25.3, 17.7, 9.3; IR (cm^{-1}, film) 3407, 1645, 1260, 1016; HRMS (ESI) calcd for $[M-H]^-$ $C_{13}H_{17}O_2$: 205.1234, found 205.1235.

Direct Access to Compound ***20*** *from* ***16***. To a solution of **16** (96 mg, 0.36 mmol) in ether (5 mL) was added $LiAlH_4$ (140 mg, 3.66 mmol) at 0 °C. After addition, the reaction was warmed to room temperature and stirred overnight. The next day, the reaction was quenched by the addition of water, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 1:1 to 1:3) afforded **20** (75 mg, 99%) as a pale yellow crystalline solid, with spectral properties identical to those reported above.

Compound ***21***. To a solution of **20** (61 mg, 0.28 mmol) in dichloromethane (3 mL) was added Et_2Zn (1 M in hexane, 0.6 mL, 0.6 mmol) at 0 °C. After 15 min, CH_2I_2 (48 μL, 0.6 mmol) was injected into the mixture. The reaction was then heated to 40 °C for 18 h and then returned to room temperature. Additional Et_2Zn (1 M in hexane, 0.6 mL, 0.6 mmol) and CH_2I_2 (48 μL, 0.6 mmol) was added, and the reaction was heated to 40 °C overnight. The following day, the reaction was cooled to room temperature and quenched by the addition of saturated NH_4Cl. The resulting mixture was extracted twice with dichloromethane, washed with brine, dried over $NaSO_4$, and concentrated in vacuo to afford **21** as a colorless oil with no further purification (63 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (d, J = 11.4 Hz, 1H), 3.68 (d, J = 4.0 Hz, 1H), 3.65 (d, J = 4.0 Hz, 1H), 3.48 (d, J = 11.3 Hz, 1H), 2.26−2.44 (m, 5H), 1.72 (dd, J = 14.1, 9.6 Hz, 1H), 1.36 (d, J = 7.4 Hz, 1H), 1.20−1.27 (m, 2H), 0.84 (dd, J = 5.0, 2.5 Hz, 1H), 0.73 (d, J = 10.5 Hz, 1H), 0.66 (ddd, J = 8.6, 4.2, 1.2 Hz, 1H), 0.05 (dd, J = 7.2, 2.8 Hz, 1H), −0.02 (dd, J = 7.2, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.0, 66.4, 52.5, 50.6, 41.7, 40.8, 37.1, 33.6, 30.6, 26.4, 24.1, 20.1, 16.2, 8.0; IR (cm^{-1}, film) 3324, 2933, 1456, 1261, 1024, 913; HRMS (ESI) calcd for $[M - H]^-$ $C_{14}H_{19}O_2$ 219.1390, found 219.1383.

Compound ***22***. To a solution of **21** (30 mg, 0.14 mmol) in a mixture of CCl_4 (0.5 mL), MeCN (0.5 mL), and water (0.75 mL) were added $NaIO_4$ (584 mg, 2.74 mmol) and $RuCl_3{\cdot}XH_2O$ (5.7 mg). The reaction mixture was stirred overnight and then was partitioned between aqueous HCl (10%) and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Chromatography (dichloromethane−methanol, 20:1) afforded **22** as a white solid (33 mg, 99%): ^{1}H NMR (300 MHz, D_2O) δ 2.50−2.55 (m, 1H), 2.32−2.48 (m, 4H), 1.80 (dd, J = 9.1, 5.1 Hz, 1H), 1.65−1.75 (m, 2H), 1.26 (d, J = 10.4 Hz, 1H), 1.19 (dd, J = 9.1, 3.0 Hz, 1H), 1.14 (t, J = 4.4 Hz, 1H), 0.83 (d, J = 11.0 Hz, 1H), 0.44 (dd, J = 7.7, 5.0 Hz, 1H), 0.37 (dd, J = 5.0, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 185.7, 184.9, 51.3, 48.2, 41.1, 41.0, 39.7, 32.2, 29.2, 28.0, 27.6, 24.0, 17.9, 12.8; IR (cm^{-1}, film) 3351, 1685, 1540, 1423, 830; HRMS (ESI) calcd for $[M + Na]^+$ $C_{14}H_{16}O_4Na$ 271.0941, found 271.0940.

Compound ***23***. To a stirred solution of trimethylsulfoxonium iodide (99 mg, 0.45 mmol) and DBU (69 mg, 0.45 mmol) in MeCN (5 mL) was added **4b** (90 mg, 0.225 mmol) in MeCN (1 mL). The reaction was heated to 60 °C for 36 h. The resulting mixture was diluted with ethyl acetate, filtered through filter paper, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (hexanes−ethyl acetate, 2:1) to afford **23** as a yellow oil (67 mg, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13−7.29 (m, 10H), 6.67 (q, J = 2.2 Hz, 1H), 5.10 (d, J = 12.7 Hz, 1H), 4.95 (d, J = 12.7 Hz, 1H), 4.89 (d, J = 12.6 Hz, 1H), 4.78 (d, J = 12.6 Hz, 1H), 3.13−3.23 (m, 1H), 2.69−2.80 (m, 2H), 2.58−2.68 (m, 1H), 2.48-2.53 (m, 1H), 2.39 (ddt, J = 18.2, 10.3, 2.7 Hz, 1H), 1.36 (dd, J = 7.6, 4.2 Hz, 1H), 1.17 (dt, J = 10.7, 1.7 Hz, 1H), 1.08 (dd, J = 5.4, 4.5 Hz, 1H), 0.84 (dd, J = 10.9, 1.0 Hz, 1H), 0.54 (dd, J = 7.7, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (2C), 143.3, 137.5, 136.4, 136.2, 128.6, 128.5, 128.1, 128.0, 66.3, 65.9, 53.9, 44.5, 40.4, 39.9, 31.2, 31.0, 25.5, 21.7, 13.8; IR (cm^{-1}, film) 2955, 1714, 1630, 1455, 1280, 1230, 1135, 746; HRMS (ESI) calcd for $[M + Na]^+$ $C_{27}H_{26}O_4Na$ 437.1723 found 437.1723.

Compound ***24***. To a solution of **23** (68 mg, 0.17 mmol) in 10 mL of MeOH was added Pd/C 10% (∼30 mg). The reaction mixture was pressurized inside a Parr reactor to 200 psi of H_2 and was stirred for 16 h. The product mixture was filtered through cotton and then concentrated in vacuo. The residue was purified by chromatography (hexanes−ethyl acetate, 2:1) to afford **24** as a white solid (30 mg, 75%, mp >200 °C): ^{1}H NMR (300 MHz, D_2O) δ 2.56−2.67 (m, 1H), 2.44−2.49 (m, 1H), 2.37−2.44 (m, 2H), 2.19−2.24 (m, 1H), 1.54−1.82 (m, 4H), 1.39 (d, J = 10.7 Hz, 1H), 1.23−1.34 (m, 1H), 1.19 (t, J = 4.6 Hz, 1H), 1.04 (d, J = 11.1 Hz, 1H), 0.52 (dd, J = 7.7, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 185.7, 185.0, 52.8, 47.3, 46.2, 39.4, 38.8, 34.2, 31.7, 28.7, 28.7, 18.7, 12.7; IR (cm^{-1}, film) 3421, 2926, 1701, 1560, 1438, 1295; HRMS (ESI) calcd for $[M + Na]^+$ $C_{13}H_{16}O_4Na$ 259.0941, found 259.0941.

DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979−8989

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01332.

^{1}H NMR and ^{13}C NMR spectra for all new compounds, 2D NMR data for **7a** and **8a**, computational results and crystallographic data(PDF)

X-ray data for compound **7a** (CIF)

X-ray data for compound **14** (CIF)

X-ray data for compound **17** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wulff@uvic.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Cancer Research Society of Canada for operating funds (17396) and the Michael Smith Foundation for Health Research (CI-SCH-03064) and the Canada Research Chairs program (950-226685) for salary support to J.W. and incentive funds used to support this research. We also thank the Office of the Vice President of Research at the University of Notre Dame for financial support for the purchase of the copper microfocus source used in this research as well as Dr. Ori Granot and the UVic Genome BC Proteomics Centre for mass spectrometry support.

■ REFERENCES

(1) Thiele, J. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 68−71.

(2) For a modification to Thiele's method, see: Ziegler, K.; Froitzheim-Kühlhorn, H.; Hafner, K. *Chem. Ber.* **1956**, *89*, 434−443.

(3) Dunn, G. L.; Donohue, J. K. *Tetrahedron Lett.* **1968**, *9*, 3485−3487.

(4) NMR data for the methyl ester analogue of **2** suggest that **2b** is the major species in solution, along with smaller quantities of **2c**. Structures analogous to **2a** were not observed but could still be present in very small quantites; see ref 5.

(5) Top, S.; Lehn, J.-S.; Morel, P.; Jaouen, G. *J. Organomet. Chem.* **1999**, *583*, 63−68.

(6) Deslongchamps, G.; Deslongchamps, P. *Tetrahedron* **2013**, *69*, 6022−6033.

(7) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: Chichester, 1976; pp 136, 167−168. (b) Fleming, I. *Molecular Orbitals and Organic Chemical Reactions, Reference Edition*; John Wiley & Sons: Chichester, 2010; pp 321−322.

(8) (a) Rebek, J.; Askew, B.; Islam, N.; Killoran, M.; Nemeth, D.; Wolak, R. *J. Am. Chem. Soc.* **1985**, *107*, 6736−6738. (b) Rebek, J.; Nemeth, D. *J. Am. Chem. Soc.* **1986**, *108*, 5637−5638.

(9) Talbiersky, P.; Bastkowski, F.; Klärner, F.-G.; Schrader, T. *J. Am. Chem. Soc.* **2008**, *130*, 9824−9828.

(10) Petitjean, A.; Khoury, R. G.; Kyritsakas, N.; Lehn, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 6637−6647.

(11) Harmata, M. *Acc. Chem. Res.* **2004**, *37*, 862−873.

(12) Sergeyev, S. *Helv. Chim. Acta* **2009**, *92*, 415−444.

(13) Robinson, J. A. *Acc. Chem. Res.* **2008**, *41*, 1278−1288.

(14) (a) Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647−650. (b) Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577−3592.

(15) Verbist, B. M. P.; De Borggraeve, W. M.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2005**, *2005*, 2941−2950.

(16) (a) Feigel, M. *J. Am. Chem. Soc.* **1986**, *108*, 181−182. (b) Winningham, M. J.; Sogah, D. Y. *J. Am. Chem. Soc.* **1994**, *116*, 11173−11174.

(17) Díaz, H.; Espina, J. R.; Kelly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 8316−8318.

(18) Brant, M. G.; Wulff, J. E. *Org. Lett.* **2012**, *14*, 5876−5879.

(19) Marchand, A. P.; Namboothiri, I. N. N.; Lewis, S. B.; Watson, W. H.; Krawiec, M. *Tetrahedron* **1998**, *54*, 12691−12698.

(20) Watson, W. H.; Marchand, A. P.; Sivappa, R. *ARKIVOC* **2004**, 66−73.

(21) Minter, D. E.; Smith, W. B.; Marchand, A. P.; Etukala, J. R.; Sivappa, R. *J. Phys. Org. Chem.* **2004**, *17*, 174−179.

(22) Gansäuer, A.; Fleckhaus, A.; Lafont, M. A.; Okkel, A.; Kotsis, K.; Anoop, A.; Neese, F. *J. Am. Chem. Soc.* **2009**, *131*, 16989−16999.

(23) Murphy, E. B.; Bolanos, E.; Schaffner-Hamann, C.; Wudl, F.; Nutt, S. R.; Auad, M. L. *Polym. Reprints* **2008**, *49*, 976−977.

(24) For a detailed analysis of the NMR spectra associated with the diester derivative, see: Minter, D. E.; Marchand, A. P.; Lu, S.-P. *Magn. Reson. Chem.* **1990**, *28*, 623−627.

(25) Peters, D. *J. Chem. Soc.* **1961**, 1042−1048.

(26) Scapens, D.; Adams, H.; Johnson, T. R.; Mann, B. E.; Sawle, P.; Aqil, R.; Perrior, T.; Motterlini, R. *Dalton Trans.* **2007**, 4962−4973.

(27) Dive, G.; Robiette, R.; Chenel, A.; Ndong, M.; Meier, C.; Desouter-Lecomte, M. *Theor. Chem. Acc.* **2012**, *131*, 1236.

(28) Marchand, A. P.; Zhao, D.; Ngooi, T.-K.; Vidyasagar, V.; Watson, W. H.; Kashyap, R. P. *Tetrahedron* **1993**, *49*, 2613−2620.

(29) Deslongchamps, P.; Cheriyan, U. O.; Lambert, Y.; Mercier, J.-C.; Ruest, L.; Russo, R.; Soucy, P. *Can. J. Chem.* **1978**, *56*, 1687−1704.

(30) Paquette, L. A.; Kearney, F. R.; Drake, A. F.; Mason, S. F. *J. Am. Chem. Soc.* **1981**, *103*, 5064−5069.

(31) Peters, D. *J. Chem. Soc.* **1959**, 1761−1765.

(32) NMR calculations were performed with Spartan '14 using EDF2 functionals with a 6-31G* basis set.

(33) Alberto also reported the formation of a ketone under similar conditions, although the connectivity of the isolated product was not established; see: Liu, Y.; Spingler, B.; Schmutz, P.; Alberto, R. *J. Am. Chem. Soc.* **2008**, *130*, 1554−1555.

(34) A small amount of aqueous KOH was used to bring **3** into D_2O for NMR analysis.

(35) Similar regioselectivity was observed during the unwanted additions of methanol during esterification and saponification of **3** and **4**. See refs 20 and 21.

(36) Peters also reported a conjugate addition of dimethylamine to **4a**; however the stereochemical outcome was not established. See ref 25.

(37) Namboothiri, I. N. N.; Rastogi, N.; Ganguly, B.; Mobin, S. M.; Cojocaru, M. *Tetrahedron* **2004**, *60*, 1453−1462.

(38) N'Dongo, H. W. P.; Liu, Y.; Can, D.; Schmutz, P.; Spingler, B.; Alberto, R. *J. Organomet. Chem.* **2009**, *694*, 981−987.

(39) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809−886.

(40) Structural calculations were performed with Spartan '14 using B3LYP functionals with a 6-31G* basis set.

(41) The presence or absence of the methyl group appears to make no significant difference to the cleft angle: the DFT-optimized structure of **4a** had a cleft angle identical to that of structure **A** (123°). Similarly, the DFT-optimized structure of **14** had a cleft angle (189°) identical to that determined for structure **D**, although the individual angles α and β varied slightly in this case.

(42) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.

(43) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323−5324. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256−4264.

DOI: 10.1021/acs.joc.5b01332
J. Org. Chem. 2015, 80, 8979−8989